

Enzymes proofread DNA during its replication and repair damage in existing DNA

- Mistakes during the initial pairing of template nucleotides and complementary nucleotides occurs at a rate of one error per 10,000 base pairs.
- DNA polymerase proofreads each new nucleotide against the template nucleotide as soon as it is added.
- If there is an incorrect pairing, the enzyme removes the wrong nucleotide and then resumes synthesis.
- The final error rate is only one per billion nucleotides.
- DNA molecules are constantly subject to potentially harmful chemical and physical agents.
 - Reactive chemicals, radioactive emissions, X-rays, and ultraviolet light can change nucleotides in ways that can affect encoded genetic information.
 - DNA bases often undergo spontaneous chemical changes under normal cellular conditions.
- Mismatched nucleotides that are missed by DNA polymerase or mutations that occur after DNA synthesis is completed can often be repaired.
 - Each cell continually monitors and repairs its genetic material, with over 130 repair enzymes identified in humans.
- In **mismatch repair**, special enzymes fix incorrectly paired nucleotides.
 - A hereditary defect in one of these enzymes is associated with a form of colon cancer.
- In **nucleotide excision repair**, a **nuclease** cuts out a segment of a damaged strand.
 - The gap is filled in by DNA polymerase and ligase.
- The importance of proper function of repair enzymes is clear from the inherited disorder xeroderma pigmentosum.
 - These individuals are hypersensitive to sunlight.
 - In particular, ultraviolet light can produce thymine dimers between adjacent thymine nucleotides.
 - This buckles the DNA double helix and interferes with DNA replication.
 - In individuals with this disorder, mutations in their skin cells are left uncorrected and

The ends of DNA molecules are replicated by a special mechanism

- Limitations in the DNA polymerase create problems for the linear DNA of eukaryotic chromosomes.
- The usual replication machinery provides no way to complete the 5' ends of daughter DNA strands.
- Repeated rounds of replication produce shorter and shorter DNA molecules.
- The ends of eukaryotic chromosomal DNA molecules, the **telomeres**, have special nucleotide sequences.
 - In human telomeres, this sequence is typically TTAGGG, repeated between 100 and 1,000 times.
- Telomeres protect genes from being eroded through multiple rounds of DNA replication.
- Eukaryotic cells have evolved a mechanism to restore shortened telomeres.
- **Telomerase** uses a short molecule of RNA as a template to extend the 3' end of the telomere.
 - There is now room for primase and DNA polymerase to extend the 5' end.
 - It does not repair the 3'-end "overhang," but it does lengthen the telomere
- Telomerase is *not* present in most cells of multicellular organisms.
- Therefore, the DNA of dividing somatic cells and cultured cells does tend to become shorter.
- Thus, telomere length may be a limiting factor in the life span of certain tissues and the organism.
- Telomerase is present in germ-line cells, ensuring that zygotes have long telomeres.
- Active telomerase is also found in cancerous somatic cells.
 - This overcomes the progressive shortening that would eventually lead to self-destruction of the cancer.